The impact of European embryonic stem cell patent decisions on research strategies

Article (Accepted Version)

Impact of European Courts' decisions on embryonic stem cells patents: toward new research strategies

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Abstract: The recent enlargement of exclusion from patentability of inventions on human embryonic stem cells (hESC) by the uniform approach of European Courts imposes a reorganization of hESC's research and development strategies.

Main text:
Patentability of inventions on human embryonic stem cells (hESC) has been recently restricted both by the European Patent Office (EPO) and the Court of Justice of the European Union (CJEU). Although they are not bound together as they rely on two different European Organizations, respectively the European Patent Organization and the European Union (EU), their decisions provide a uniform exclusion of patent on hESC obtained via the destruction of human embryos (Table 1).

Context
On 25 November 2008, in the *Wisconsin Alumni Research Foundation* case (here after the *WARF* case), the enlarged board of appeal of the EPO (here after the enlarged board), [1] considered that the non-patentability of inventions using human embryos for industrial or commercial purposes forbids to grant European patents to products which could be prepared, at the filing date and as described in the patent' claims, exclusively by a method destroying necessarily an embryo. While it decided that products prepared *exclusively* by a method involving the destruction of human embryos, at the patent filing date, are not patentable, the enlarged board let open a possibility of patent for products and methods using hESC available in biobanks as previously derived from hESC lines.[2]

On 18 October 2011, in the *Brüstle v Greenpeace eV* case (here after the *Brüstle* case)[3] the CJEU broadly interpreted the patent's exclusion for uses of human embryos for commercial or industrial purposes. First, it defined widely the notion of human embryo as "any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis". Second, it excluded from patentability an invention where the technical teaching of the patent application requires the prior destruction of human embryos or their use as base material, whenever such destruction takes place and even if the claims' description does not refer to human embryos' use. Most scientists acting in the field of hESC research have been worried by the *Brüstle* case as it prohibits hESC's patents that could be obtained in the USA or Asia.[4]

The *Technion* case

On 4 February 2014, in the *Technion Research and Development Foundation* case (here after the *Technion* case),[5] the technical board of appeal of the EPO (here after the technical board) decided to align with the *Brüstle* case instead of keeping the door open by its own organization in the *WARF* case. The *Technion* case was brought up by a company established in Israel, a State which is neither part of the European Patent Organization nor of the EU. The Technion Company applied to obtain a European patent on a cell culture comprising both human foreskin cells and hESC as well as on methods of maintaining hESC in an undifferentiated state. The patent was refused by the examining division of the EPO because hESC lines used to carry out the invention were not publicly available at the filing date of application. Thus, it considered the only possibility to obtain the hESC necessary to realize the claimed method relied on the destruction of human embryos. Following the company's appeal, the technical board of the EPO adopted its decision: although serious doubts remain on the public availability of the hESC lines described in the application, it decided to maintain the patent's refusal on the basis of the necessary prior destruction of human embryos to establish the cell lines.
The two main arguments used by the company Technion were rejected by the technical board. On the one hand, it was not possible to pass through the door let open in the *WARF* case: using methods based on commercially or otherwise publicly available hESC lines which do not involve *de novo* destruction of human embryos do not prevent the exclusion from patentability. Indeed, although the technical board examined the cell lines claimed to be publicly available at the date of application, they all resulted from the initial destruction of human embryos through the use of the inner cell mass of blastocyst for their derivation. It also noted that no evidence on file proved that hESC lines allegedly available from the US NIH were obtained by methods which do not involve the destruction of human embryos.
On the other hand, the argument of a too wide exclusion because of the consideration of all the steps prior to an invention was considered irrelevant as in the *WARF* case. Indeed, the invention has to be viewed globally without singularizing persons involved or points in time of the different steps resulting in the invention at stake. In such context, the technical board in the *Technion* case considered that all steps preceding the invention were "a necessary precondition for carrying out the claimed invention".
Thus, the exclusion from patentability is considered extensively in the *Technion* case which is in line with the *Brüstle* ruling of the CJEU while closing the door let opened by the *WARF* case. Indeed, the *Technion* case excluded from patentability "inventions which make use of [hESC] obtained by *de novo* destruction of human embryos or of publicly available hESC lines which were initially derived by a process resulting in the destruction of the human embryo".

With the *Technion* case, a better uniformity of European patent law is clearly and legally settled between the EPO and the EU.[6] Both for European patents under the EPC, and for national patents within the EU Member States which have to implement the *Brüstle* case, it will be applied that hESC technologies will not be patentable if the used hESC are obtained from the destruction of human embryos whenever is the point in time at which such destruction takes place.

Arguing patentability refusal on hESC research pathways
Surely the *Brüstle* case[7] and even more, the *Technion* case will have an impact on the organization of hESC innovation pathways as it covers the whole Europe beyond the EU Member States. However, the positive or negative influence of such decisions on hESC research as arguments, are balanced (Table 2). Indeed, regarding hESC research financing, the fear of private investments diminution[8] can be nuanced by the fact that fundamental research

should not be directly impacted by decisions related to patenting and is mainly funded by public institutions. It should be highlighted that, explicitly from 2006, the EU does not fund research activities that destroy human embryos including for the procurement of stem cells, although it funds the subsequent steps involving human embryonic stem cells.[9] It has been argued that societies and researchers (whom careers partly rely on patents obtained) will move towards more liberal countries where financing are available.[10] However the opposite may also be true: American Biotechnologies societies may move to Europe to escape patents burden in the USA or in Asia[11] The exclusion from patentability may also delay medical applications as an impediment to the commercialization of cell therapies based on hESC[4, 8] whereas it may also have no major impact[7] in this area. Furthermore such decisions may be seen as expressing that hESC research is considered immoral[11] whereas science regulation and intellectual property should not get mixed up.[7] Moreover, in such a context of legal clarification on patentability with stem cells, some argued they never thought it will be possible to obtain patent on hESC in case of embryo destruction.[11] It can also be considered these legal decisions have a limited impact in the lights of future technological developments: [12] it is still possible to obtain patents where hESC are obtained without embryo destruction[13] and IPS may provide new patent possibilities. While patents as such can be seen as necessary for investors, notably as they limit secrecy, patents' unavailability permits higher freedom of activities (no fear of patents' rights infringement, no royalties to pay for exploitative license) and other means to stimulate innovation can be used. The latter can be scientific (not so easy to copy in the field of hESC, protection by process to deliver cells or to control the quality in manufacturing),[4] regulatory (data protection, marketing authorization, other incentive legislations on biosimilars or on orphan drugs) and economic (commercial secret, incentive tax).[7]

The imperative reorganization of research and development strategies

The exclusion from patent of hESC cell lines, where they have been obtained through the destruction of human embryo whenever such destruction takes place, is now a certainty in Europe as it is based on two distinct legal bases: the CJEU and the EPO decisions. It can be considered as having an ethical basis, rather than a technical one. Such ethical barrier to patentability is also exhibited in the 2013 decision of the US Supreme Court on the patentability of genes which excluded isolated DNA naturally produced from patentability.[14] There seems to be a clear difference done between research to generate knowledge and patents that are intended to generate commercial activities.

It is now realistic to consider that most of the hESC lines worldly available at the moment cannot be used to obtain patents in Europe. To obtain patent in the field of hESC, researchers will have to use hESC lines derived without destruction of human embryo, or IPS lines, although the equivalence between the two sources is not established. To this end, it could be recommended to hESC repositories to address clearly the techniques used for obtaining the lines and to make this information available to researchers. Another possibility could be to require this information to be systematically described, as a standard, in the European hESC registry. However, if using hESC lines derived without destruction of human embryo avoid the ethical problem of the destruction of potential human being it does not solve that of using embryo for commercial and industrial purposes. The issue of non-commercialization of the human body is major, with reference to the context of human organs trafficking and it is emphasized with hESC compared to adult stem cells. That is why, the derivation of IPS lines is a research direction widely explored at the moment. Indeed, if focusing on IPS while using hESC as "a gold standard" brings to conclusive results for medical applications, legal decisions on non-patentability of hESC from destructed embryos will have less consequence on innovation. If not, incentives for hESC could be re-opened through patent, based on

utilitarian reasoning and patient benefit otherwise unattainable, although this is far to be probable. In any cases, both ways would take years of research. Thus, hESC research towards innovation faces a re-organisation imperative, as one route for future exploitation is clearly blocked in Europe, whereas doubts were permitted before the *Technion* case. This impacts on research strategies; it requires a more profound re-organisation from companies who had bet on patenting hESC lines and organized accordingly their long term business plan. It rather gives an advantage to those who had invested at a rather short term without building primarily on such patents. It is now necessary to find new strategies of innovation that do not rely on patent. They can rely on other existing tools such as the scientific, regulatory and economic ones above-mentioned or they can rely mainly on national strategies, applying only to national patents without envisaging European level patenting. So far, in Germany for example, the precise description of a method which does not destroy embryo is not required by the German Federal Court to grant a patent.[15] However, this is limited to national patents and can only be a short term strategy. As a matter of fact, it can be anticipated that the restrictive approach exhibited in the *Technion* case will also be retained to grant the future European patents with unitary effect as it will also be delivered by the EPO.

<table>
<tr><th>Organisations</th><th colspan="2">European Patent Organisation</th><th>European Union</th></tr>
<tr><td>Main legal texts</td><td colspan="2">European Patent Convention[16]</td><td>Directive 98/44/EC on the legal protection of biotechnological inventions</td></tr>
<tr><td>Patents scope</td><td colspan="2">European patents</td><td>National patents</td></tr>
<tr><td rowspan="2">Legal bodies</td><td colspan="2">European Patent Office</td><td rowspan="2">Court of Justice of the European Union
Grand Chamber</td></tr>
<tr><td>Enlarged Board
(higher board)</td><td>Technical Board</td></tr>
<tr><td>Cases</td><td>WARF case
25 November 2008</td><td>Technion case
4 February 2014</td><td>Brüstle case
18 October 2011</td></tr>
<tr><td>Exclusion of hESC's patents</td><td>-necessary destruction of human embryos
-at the patent's filing date</td><td>-destruction of human embryos
-whenever the destruction takes place</td><td>-destruction or use as a base material of human embryos
-whenever the destruction takes place</td></tr>
<tr><td>Cases territorial implementation</td><td colspan="2">All contracting States to the European patent Convention
28 EU Member States + 9 other countries</td><td>28 EU Member States</td></tr>
</table>

Table 1: Recent European cases on the exclusion of patentability of hESC in Europe

	Negative impact on hESC research	Positive or neutral impact on hESC research
Research Financing	Fear of investments decrease	Fundamental research mainly funded by public institutions
Patents characteristics	Necessary for investors More secrecy without patent	Higher freedom of activities Other scientific, regulatory and economic instruments to be used
Companies and Researchers moving	Moving to more liberal countries where financing are available	Biotechnology companies may move to Europe to escape patents burdens in the USA or in Asia
Medical applications	Delayed Burden to the commercialization of cell therapies based on hESC	No major impact as health protection systems foster existing treatments' access whether patented or not
Ethics	Immorality of hESC research	Difference between science regulation and intellectual property Legal clarification: nobody thought it would be possible to obtain patent on hESC if embryo destruction, but a doubt was maintained
Legal decisions scope	No patent on hESC where destruction of human embryo	Limits in the lights of the technological developments : Still possible to obtain patents where hESC obtained without embryo destruction, new possibilities with IPS

Table 2: The balance of arguments on patent exclusions' influence on hESC research

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Acknowledgements: We would like to thank Karoline Holz for her help in the understanding of the German federal Court case law. This work has been partially supported by REGenableMED, UK ESRC Project ES/L002779/1, and by EUCelLEX FP7 program, Grant agreement N° 601806.